Remarks

Claims 1-27 are pending. New claims 26 and 27 have been added. Therefore, claims 1-27 and are under consideration. Claim 1 is amended herein to recite "wherein the nutritional supplement is not prepared as nutritional food." Support for the amendment to claim 1 can be found at least on page 10, lines 3-10. The Examiner is respectfully reminded that applicants are allowed to specifically disclaim limitations that are positively recited in the specification. In re Johnson, 588 F.2d 1008, 1019, (CCPA 1977). Applicant believe that the amendments made herein do not constitute new matter or raise new issues.

35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-25 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. In particular, the Examiner alleges that "while being enabling for delaying the onset or slowing the progression of hypertension in a subject, does not reasonably provide enablement for the prevention of the hypertension." Applicants respectfully traverse this rejection.

Applicants respectfully remind the Examiner that the standard for enablement is whether the claimed invention coupled with the information known in the art enables one of skill in the art to make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir.1988). Furthermore, with respect to determining undue experimentation, "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

In determining whether experimentation is undue, the Federal Circuit in *In re Wands* provided a non-exclusive list of factors for determining undue experimentation including 1) the breadth of the claims; 2) the nature of the invention; 3) the state of the prior art; 4) the level of one of ordinary skill; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor; 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the disclosure. Here, the claims are drawn to

"methods for preventing or delaying the onset of or slowing the progression of hypertension in a subject." As the Examiner has conceded that Applicants have enabled delaying the onset and slowing the progression of hypertension, only the prevention of hypertension need be addressed (see page 2, first paragraph of the present office action). Applicants note that the Examiner points to paragraphs 66-72 of the present application as indicating that hypertension was not prevented because allegedly treatment was not commenced until after the onset of hypertension. Applicants respectfully note that although the Examiner's argument is based on the age of the mice when quercetin treatment began and the generalized age of the animals when hypertension begins, this argument is not based in fact. In particular, as noted in paragraphs 66-72, quercetin treatment began at week five post birth. Applicants further note that in Figure 5A, the systolic and diastolic pressure of the quercetin was first measured at 6 weeks post birth. Applicants point out that in both treated and untreated groups, systolic and diastolic pressure had not risen to hypertensive levels at week six as defined on page 8, lines 1-8 of the specification. Specifically, the specification defines hypertension as systolic pressure above 140 and diastolic pressure greater than 90. Importantly, the animals in the present experiments had not attained such levels at 6 weeks (i.e., 7 days after quercetin administration began). Accordingly, treatment had begun prior to seven days before the onset of hypertension. Moreover, as noted in Figure 5 the systolic and diastolic pressure in treated animals never rose beyond a statistical amount over the baseline measurement. Applicants also note that Figure 1 shows that mice that received nutritional supplement before adominal aorta constriction showed no increase in arterial pressure relative to mock controls. Furthermore, Applicants show that prior treatment with quercetin resulted in the prevention of Akt activation and a reduction of ERK1/2 which is relevant as Akt activation and increase in ERK1/2 have been implicated in cardiac hypertrophy (see Figure 4 and the corresponding legend in paragraph 15). Accordingly, Applicants have indeed prevented hypertension contrary to the assertions of the Examiner and provided sufficient guidance and examples to enable the scope of the invention.

The Examiner further asserts that Carlstrom et al. is evidence that the disclosed methods do not work and therefore are not enabled. Applicants note that in addition to the fact that the enclosed figures and examples show the claimed methods do work, the Examiner's reliance on Carlstrom et al. is misplaced. In particular, Carlstrom et al. note that quercetin supplied as part

of the feed was not a successful delivery method due to the in ability to regulate intake in a free feed system where the animal controls food intake. However, as the Examiner notes Carlstrom et al. do acknowledge that oral gavage (i.e., forced feeding) was successful as a route of administration. Despite Carlstrom not truly commenting on the enablement of the claims; and in an effort to further prosecution, Applicants have amended claim 1 to recite "wherein the nutritional supplement is not prepared as nutritional food." Thus, the presently claimed methods do not rely on feed supplied supplements and any conclusions drawn from Carlstrom regarding the claims as presently amended only support the enablement of all embodiments. Applicants also note that The Applicants believe this rejection to be overcome and respectfully request its withdrawal.

The Examiner has rejected claims 1-28 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that thee specification does not provide support for the recitation "wherein the nutritional supplement is administered to the subject for at least seven days prior to the onset of hypertension." Applicants respectfully traverse the rejection. Applicants respectfully point out that the standard for written description is whether the description clearly allow one of skill in the art to recognize that the inventor invented what is claimed. In re Gosteli, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Applicants note that the Examiner concedes that the specification teaches in Example 1, that hypertension was surgically induced 8 days after daily quercetin treatment had commenced. Moreover, Applicants note that Figure 5A and Examples VII and VIII show that quercetin treatment began at week five and in control mice the onset of hypertension had not occurred until after 6 weeks of age. Thus, the specification provides at least two specific recitation of administering quercetin at least seven days prior to the onset of hypertension. Thus, for at least this reason the written description requirement has been met.

Additionally, Applicants note the Examiner seems to be focused on the phrase "at least seven days prior" and cites case law which discusses the standard for written description with respect to ranges. Applicants respectfully point out that these recitations of the law are misplaced in the present case as the present claims do not cite a range. In particular, Applicants cite a starting point for treatment to occur before a set time. Applicants do not state that treatment occurs between certain points or starts only within a set period of days as would be

appropriate for a range. By contrast, Applicants claim a singular time point for which administration of quercetin must begin. Applicants provide at least two examples in the specification where treatment commenced prior to seven days. Because Applicants have provided in the specification multiple examples and disclosure of treating with quercetin prior to the onset of hypertension, Applicants believe this rejection has been overcome and respectfully request its withdrawal.

35 U.S.C. § 102

The Examiner has rejected claims 1-3, 7, 8, 10, 14-16, 27, and 28 under 35 U.S.C. § 102(a) as allegedly being anticipated by Duarte et al. (2002) *J. Hypertension* 20: 1843-1854. In particular, the Examiner contends that Duarte et al. disclose "administration of 10mg/kg/day quercetin in 1% methylcellulose oral gavage was effective in inhibiting the development of hypertension." However, the Examiner makes no mention regarding the time of administration of quercetin and the onset of hypertension. It is a long established tenet of patent law that in order for a reference to anticipate the claim, it must teach each and every limitation of the claim. Applicants respectfully point out that, as amended, claim 1 is drawn to "A method for preventing or delaying the onset of or slowing the progression of hypertension in a subject, said method comprising administering to a subject a nutritional supplement ...wherein the nutritional supplement is administered to the subject for at least seven days prior to the onset of hypertension." Respectfully, Duarte et al. does not teach the administration of quercetin prior to the onset of hypertension as is now claimed. Specifically, on page 1846 of Duarte et al. the authors note that quercetin treatment was concomitant with induction of hypertension by L-NAME (see column 1, paragraph 3, page 1846). Moreover, as noted by Gardiner et al. (1990) *Br. J. Pharmacol* 101:10-12 (abstract of which is submitted herein as Exhibit A), hypertension results within 9 hours of L-NAME administration. Thus, at best, the quercetin administration of Duarte et al. occurred a mere nine hours prior to the onset of hypertension. For at least these reasons, Duarte et al. fails to teach all the limitations of the claims. Therefore, Duarte et al. does not anticipate claims 1-3, 7, 8, 10, 14-16, 27, and 28. Applicants believe this rejection has been overcome and respectfully request its withdrawal.

35 U.S.C. § 103

The Examiner has rejected claims 1-25 under 35 U.S.C. § 103(a) as being unpatentable over Duarte et al. in view of Wakat (U.S. Patent No. 6,054,128), Duarte et l. (2001), and Schmitz et al. ((U.S. Patent No. 6,610,320). Applicants respectfully traverse the rejection. In the recent KSR Int'l Co. v Teleflex, Inc. ruling, the Supreme Court has reaffirmed the *Graham* factors for determination of obvious under 35 U.S.C. 103(a). *KSR Int 'l Co. v. Teleflex, Inc. (KSR),* No 04-1350 (U.S. Apr. 30, 2007). The three factual inquiries under *Graham* require examination of: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art. *Graham v. John Deere (Graham),* 383 U.S. 1, 17-18, 149 USPQ 459, 467 (1966). Additionally, the court in Graham noted a fourth consideration for the determination of obviousness would be any objective evidence of secondary considerations such as unexpected results, unmet need in the art, and commercial success. Furthermore, in order to establish a prima facie case of obviousness, the examiner has the initial burden of supporting the conclusion of non-obviousness. In particular, the Examiner has the initial burden of ascertaining the differences between the claims and the prior art which requires interpreting both the art and the claims as a whole. Put another way, "all words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Applicants respectfully assert that the prior art alone or in combination does not teach all the limitations of the claims. As Applicants have demonstrated above, Duarte et al. (2002) does not teach all limitations of the claim. Specifically, Duarte et al. does not disclose the administration of a nutritional supplement at least seven days prior to the onset of hypertension. Similarly, Duarte et al (2001) does not disclose administration of a nutritional supplement at least seven days prior to the onset of hypertension. As noted in the prior response to office action, Duarte et al. (2001) utilizes a spontaneously hypertensive rat, and quercetin was not administered to said rats until 12 weeks of age which was after hypertension was present in the animals. Thus, Duarte et al. (2001) also fails to disclose the administration of a nutritional supplement at least seven days prior to the onset of hypertension. Therefore, the Examiner must rely on the combination of Wakat and Schmitz to disclose this deficiency. The Examiner cites Wakat for the alleged teaching of "the combination of quercetin with other nutrients." Applicants

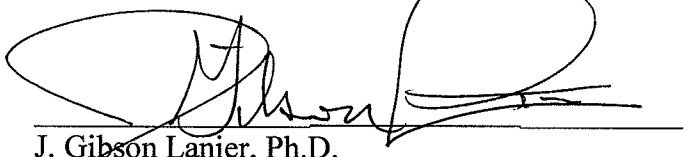
respectfully note that Wakat, as with Duarte, does not disclose let alone teach the administration of a nutritional supplement comprising quercetin at least seven days prior to the onset of hypertension. Regarding Schmitz et al., Applicants respectfully note that nowhere in Schmitz et al. is disclosed the administration of quercetin let alone the administration of quercetin at least seven days prior to the onset of hypertension. Specifically, Applicants note that Schmitz et al. relates to the treating or prevention of atherosclerosis through the use of catechin not quercetin as is claimed herein. Moreover, as with the other cited references, Schmitz et al. does not disclose the prior administration of a nutritional supplement comprising quercetin at least seven days before the onset of hypertension. Furthermore, as quercetin and catechin are different chemical compounds it would be scientifically improper to assert any finding related to one upon the other. Thus, alone or in combination, the cited art fails to disclose all the limitations of the claims which is necessary to establish an claim of obviousness when the claim as a whole is considered. Accordingly, Applicants believe that the Examiner has not met the necessary requirements to establish a prima facie case of obviousness. Applicants believe this rejection has been overcome and respectfully request its withdrawal.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A credit card payment in the amount of $515.00 is being submitted electronically, representing $245.00 the small-entity fee for a two (2) month Extension of Time under 37 C.F.R. § 1.17(a)(2), $270.00 the small entity fee for a Notice of Appeal, Notice of Appeal, and the Request for a two (2) month Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

BALLARD SPAHR ANDREWS & INGERSOLL, LLP



J. Gibson Lanier, Ph.D.
Registration No. 57,519

BALLARD SPAHR ANDREWS & INGERSOLL, LLP
Customer Number 23859
678-420-9300
678-420-9301 (fax)

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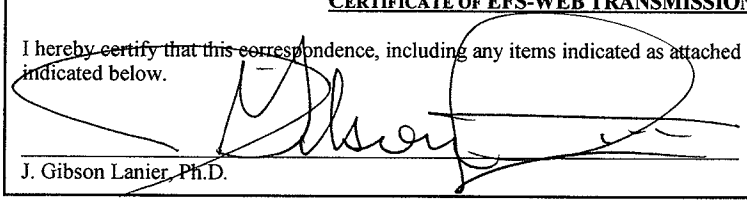

J. Gibson Lanier, Ph.D.

2/23/09
Date

1: Br J Pharmacol. 1990 Sep;101(1):10-2.

Regional haemodynamic changes during oral ingestion of NG-monomethyl-L-arginine or NG-nitro-L-arginine methyl ester in conscious Brattleboro rats.

Gardiner SM, Compton AM, Bennett T, Palmer RM, Moncada S.

Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Nottingham.

Homozygous Brattleboro (i.e. vasopressin-deficient) rats were chronically instrumented with pulsed Doppler probes and intravascular catheters to permit continuous monitoring of regional haemodynamics. Over a 9 h period, rats drinking water showed no systematic changes in heart rate or mean arterial blood pressure although renal, mesenteric and hindquarters vascular conductances fell. These changes showed diurnal rhythms, probably related to the nocturnal habits of rats. In separate groups of animals spontaneous oral ingestion of NG-monomethyl-L-arginine (L-NMMA; 1 mg ml-1) or NG-nitro-L-arginine methyl ester (L-NAME; 0.1 mg ml-1) caused marked hypertension but no significant bradycardia. Compared to control animals, rats drinking L-NMMA for 9 h showed significantly greater mesenteric and hindquarters vasoconstrictions, and rats drinking L-NAME showed greater vasoconstrictions in all 3 vascular beds.

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EXHIBIT A